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14. ABSTRACT

Patients with spinal cord injury (SCI) commonly have sleep-disordered breathing due to obstructive sleep apnea (OSA) and/or nocturnal hypoventilation (NH) due to respiratory muscle weakness. In the general population, OSA has been linked to excess cardiovascular morbidity, glucose intolerance, obesity, and hyperlipidemia, problems which are common co-morbidities with SCI. The impact of sleep-disordered breathing in SCI has received little attention. The conventional method for diagnosing sleep-disordered breathing is a facility-based polysomnogram (PSG), which is often unavailable to SCI patients because logistical obstacles limit their access to sleep laboratories. Our hypothesis is that unrecognized sleep-disordered breathing is common, can be diagnosed by home-based testing, and contributes to the morbidity of patients with SCI. This project is a prospective cohort study of 100 subjects with C1-T6 SCI. Sleep-disordered breathing will be assessed in subjects' homes with a limited PSG combined with overnight oxygen saturation (SpO2)/transcutaneous pCO_2 (tc- pCO_2) monitoring. OSA and NH will be treated with noninvasive ventilatory support according to usual standards of care. Subjects will be followed prospectively for 1 year with periodic laboratory studies, quality of life surveys, and daily symptom/event logs. Our specific aims are: 1A: Determine the prevalence of OSA and NH in SCI patients. 1B. Establish the feasibility of home-based PSG's with SpO_2/tc- pCO_2 monitoring in SCI patients. 2A: Determine whether there are reliable clinical predictors for OSA or NH, and for compliance with noninvasive ventilation. Determine the impact of early recognition and treatment of OSA and NH on: 3A. quality of life, 3B. pulmonary morbidity, 3C. blood pressure instability, and 3D. features of the "metabolic syndrome" (obesity, diabetes, hyperlipidemia). At the completion of year 1, we have 1. obtained all institutional and DoD regulatory requirements to begin the project. 2. enrolled 34 subjects, which places us ahead of pace to reach full enrollment. 3. studied 15 subjects who have successfully completed their home sleep study/SpO_2-tc- pCO_2 monitoring. Of these first 15 subjects, 100% were found to have OSA and 13.3% had NH.

15. SUBJECT TERMS
Spinal cord injury, sleep-related breathing disorder, sleep apnea, hypoventilation

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PROGRESS REPORT-YEAR 1

INTRODUCTION Patients with spinal cord injury (SCI) commonly have sleep-disordered breathing, often caused by closure of the upper airway (obstructive sleep apnea; OSA). Another form of sleep-disordered breathing in SCI is nocturnal hypoventilation (NH) due to respiratory muscle paralysis and/or reduced ventilatory drive during sleep. If sufficiently severe, either form of sleep-disordered breathing can cause decreased blood levels of oxygen (pO_2) and increased levels of carbon dioxide (pCO_2). In the general population, OSA is associated with increased risk for myocardial infarction, stroke, congestive heart failure, and the "metabolic syndrome" (increased visceral fat, hypertension, glucose intolerance, and hyperlipidemia). We know very little about the adverse clinical consequences of OSA or NH in SCI. Increased cardiovascular morbidity, diabetes and obesity are all common in SCI, supporting the <u>hypothesis underlying this proposal</u>: Unrecognized sleep-disordered breathing is common in SCI, adversely affects quality of life (QoL), and contributes to many of the co-morbidities associated with SCI.

Standard sleep studies (polysomnograms; PSG) monitor airflow, chest movement, and oxygen desaturation to detect interruptions in breathing, but pCO_2 measurements are not done routinely, so nocturnal hypoventilation with CO_2 retention may still go undetected. Data on sleep-disordered breathing in SCI has been collected largely from studies performed in sleep laboratories. Unfortunately, PSG are often not done at all in SCI because patients refuse or are denied reasonable access to sleep laboratories (wheelchair-accessibility and facilities for SCI care, accommodations for caregivers). Therefore, it is likely that clinically significant sleep-disordered breathing often goes unrecognized in SCI patients. Recent technological advances now enable us to collect valid data from home-based studies for both OSA and NH. The potential advantages of home-based testing include improved convenience/acceptance by patients and families, increased diagnostic yield, and reduced cost. <u>Our hypothesis is that sleep-disordered breathing can be diagnosed reliably and efficiently in SCI patients by home-based testing.</u>

This project is a prospective cohort study of 100 subjects with C1-T6 SCI. Sleep-disordered breathing will be assessed in subjects' homes with a limited PSG combined with overnight oxygen saturation (SpO_2)/transcutaneous pCO_2 (tc- pCO_2) monitoring. OSA and NH will be treated with noninvasive ventilatory support according to usual standards of care. Subjects will be followed prospectively for 1 year with periodic laboratory studies, quality of life surveys, and daily symptom/event logs. Once sleep-disordered breathing is identified, current standards of care would be applied to determine treatment with noninvasive ventilatory support. The specific aims are:

Aim 1: A. Determine the prevalence of OSA and NH in ventilator-independent SCI patients. B. Establish the feasibility of unsupervised home-based PSG with overnight SpO_2/tc-pCO_2 monitoring to diagnose sleep-disordered breathing in SCI patients.

Aim 2: Determine whether there are reliable clinical predictors for A. the presence of OSA or NH, and B. compliance with noninvasive ventilatory support.

Aim 3: Determine how early recognition and treatment of sleep-disordered breathing affects A. quality of life, B. pulmonary morbidity, C. autonomic dysfunction (blood pressure instability), and D. features of the metabolic syndrome (obesity, diabetes, hyperlipidemia).

KEY RESEARCH ACCOMPLISHMENTS

<u>Preparation for beginning the study protocol (SOW tasks 1-8):</u>

1. Human subject approvals were obtained from the University of Michigan and the Department of Defense Office for Human Subject Protection. 2. All necessary equipment was obtained and certified for

use by biomedical engineering. 3. A study coordinator was hired. 4. Database software was obtained and secure data storage was established.

Recruitment (SOW tasks 1-8):
We received clearance to start recruiting subjects on March 2, 2012. As of Sept. 30, 2012, 34 subjects have been recruited, provided informed consent, and commenced the study protocol. Forty (40) other potential subjects were contacted, and either i) were ineligible (15), ii) refused to enroll (11), or iii) are still considering enrollment or have verbally agreed, but have not yet given written informed consent (14). This places us well ahead of schedule for reaching the target enrollment of 100 subjects by June 2014, which is the latest point when a subject can be recruited and expect to complete the entire study protocol before the study end date.

Study Protocol (SOW tasks 1-8)
After consent is obtained, the first phase of the study protocol is a 4 month period where subjects keep daily symptom/event logs. These data provide the pre-diagnosis/treatment baseline for SOW tasks 6 and 7. Fifteen subjects have completed this phase, and all have been compliant with keeping complete logs.

All 15 of the subjects that have reached the Time 0 point of the study protocol have completed the Time 0 protocol on schedule (laboratory studies, pulmonary function testing, clinical assessment, completion of quality of life questionnaires, and home-based sleep studies with tc-pCO_2/SpO_2 monitoring). The findings are summarized below.

One subject completed the Time 0 testing, but has since developed acute respiratory failure requiring tracheostomy and mechanical ventilation at an outside hospital. Per protocol, this subject is now ineligible for further participation in the study.

Adverse events, incidents, protocol violations
There have been no adverse events or subject complaints related to any phase of the study thus far. The subjects have all been fully compliant with the provisions of the study, and there have been no violations of protocol (missed studies, omissions in completing questionnaires or testing). Three (20%) of the home-based sleep studies and 2 (13.3%) of the tc-pCO_2/SpO_2 monitoring procedures provided insufficient data due to a displaced probe or equipment failure. Per protocol, these studies were repeated and were completed successfully.

PRELIMINARY DATA

Relevant co-morbidities identified at time 0 (baseline data for SOW tasks 6- 8): n=15
Hypertension: 6, dyslipidemia: 9, both hypertension and dyslipidemia: 6
Previously diagnosed glucose intolerance or overt diabetes mellitus: 2
Previously undiagnosed diabetes or glucose intolerance identified at Time 0 testing: 6

Symptoms/Events self-recorded during months -4 to 0. n=15
4 (26.7%) of subjects reported pulmonary events requiring a change in treatment.
7 (46.7%) of subjects reported dizziness or documented hypotension .
4 (26.7%) of subjects reported symptoms of autonomic dysreflexia or documented blood pressure elevations.

Home-based monitoring reliability (SOW task 2). As noted above, 3 of the 15 (20%) Stardust II home sleep studies performed to date provided insufficient data, requiring that this portion of the study be repeated. While this does not negatively impact the ultimate reliability of the studies, it does affect the

efficiency of this home-based monitoring strategy. The manufacturer serviced the Stardust II units in question, and there have been no further such episodes. Overnight tc-pCO_2/SpO_2 monitoring led to inadequate data collection on 2 occasions. These events probably occurred because of probe displacement, since there have been no recurrences while using the same monitors. While it is too early to compile meaningful data, it appears, as predicted, that the failure rates of the home-based sleep studies and are low enough that our approach to home-based testing will prove to be practical for patient use.

Home-based monitoring: prevalence of obstructive sleep apnea and nocturnal hypoventilation (SOW task 1). To date, 15 subjects have had their home-based overnight monitoring with the Stardust II sleep system and the tc-pCO_2/SpO_2 monitor. Of these, all 15 (100%) had obstructive sleep apnea, based on an obstructive apnea/hypopnea index (OAHI) > 5 events/hr, as defined in the study protocol. A predominance of obstructive apneas and hypopneas were seen in the majority of subjects, as well as hypopneas that could not be classified as obstructive, and were therefore re-classified with nocturnal hypoventilation. Central apneas were seen a few cases as well, but these are being included with non-obstructive hypoventilation, per the study protocol. The severity of obstructive sleep apnea, as determined by the OAHI, is quite variable (Figure 1). We expect that the high prevalence of obstructive sleep apnea in the study population, and the relatively low number of subjects studied to date, account for presence of obstructive sleep apnea in all of our first 15 patients to have home sleep studies. In addition, this group of patients is relatively old (mean age 51.9) and obese (by spinal cord injury standards; BMI 26.9), increasing the risk for OSA. Lastly, when we began enrolling subjects, we had, in effect, a waiting list of patients in the University of Michigan Spinal Cord Injury Model System (our recruiting base) who learned of our study through the model system patient information network. These patients eagerly sought to enroll because they had sleep apnea symptoms but were unable to have a formal polysomnogram. Therefore, our earliest data may be skewed toward subjects with the most symptomatic sleep apnea, but we expect that this effect will diminish as we recruit more patients. We are confident that this does not reflect a technical error in the sleep studies themselves, or our diagnostic criteria. Dr. Schotland, our sleep specialist, has determined that all of the studies she reviewed have yielded high quality raw data. Further, our diagnostic criteria are actually more stringent than are used in standard sleep study interpretations. Per the study protocol, we re-classify events that would normally be scored as obstructive hypopneas if the nasal air flow or chest wall movement signals, which may be compromised by spinal cord injury, are insufficient for a certain diagnosis. For this reason, our OAHI measurements represent the frequency of clear-cut obstructive events (23.2 ± 3.99 events/hr, mean ± SEM), while all other events are re-classified with non-obstructive hypoventilation. The standard AHI, which would ordinarily be used to diagnose OSA, was far higher before re-scoring (37.8 ± 5.3 events/hr; $p<0.002$), as shown in Figure 2. Further, our data reflects the number of events per hour of monitoring, rather than per hour of EEG-confirmed sleep time (as in a standard full polysomnogram). Significant periods of wakefulness during the monitoring period would artifactually lower the AHI or OAHI, so we do not believe that our threshold for a diagnosis of obstructive sleep apnea is set too low. For these reasons, we plan to continue with our current protocol, and we expect that the prevalence of obstructive

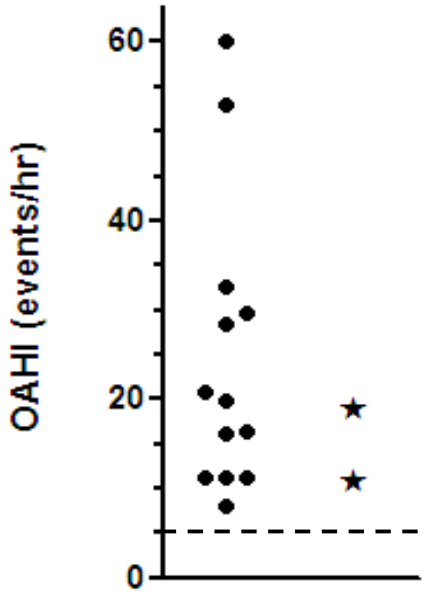

Figure 1. Scatter plot of OAHI (obstructive apnea/hypopnea index) values from the 15 subjects that have had sleep studies. The ★ indicates subjects that were also hypercapnic during sleep. The dashed line indicates the threshold for BiPAP treatment

sleep apnea will continue to be very high, but fall below 100% as we accrue more sleep studies. This preliminary analysis also highlights the likelihood that standard, automated interpretations of sleep studies may be misleading in SCI patients, and revised diagnostic criteria, such as our OAHI, may be preferable. We plan to investigate this point further and prepare these observations for publication once more subjects have been studied.

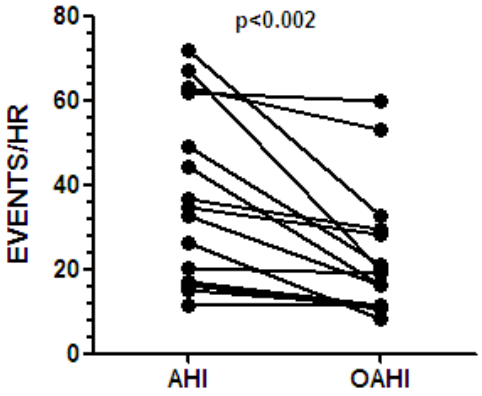

Figure 2. The standard AHI was re-calculated according to our study protocol to exclude events that normally would be scored as obstructive hypopneas, but were questionable because of low nasal air flow or chest wall movement due to spinal cord injury. The re-classified AHI is the obstructive (O)-AHI. Each pair AHI/OAHI represents the data from a single subject.

Nocturnal hypercapnia (tc-pCO_2 $\geq$ 50mmHg for $\geq$ 5% of the study time) was detected in 2 of the first 15 subjects (13.3%). This prevalence is lower the 62.5% than we saw previously in a selected population of 16 spinal cord injured patients (reference cited below). Starting noninvasive ventilation on these earlier patients excluded them from participating in the present study, so we may have temporarily skewed the subject pool away from those with the highest likelihood of nocturnal hypercapnia. We will probably have to accrue a significantly larger number of patients before we can establish a reasonably accurate prevalence for nocturnal hypercapnia.

REPORTABLE OUTCOMES

Our results thus far suggest that we will be able to satisfy the specific aims of the project. The symptom/event logs and quality of life data are being collected per protocol, the co-morbidities of SCI are being detected with the expected frequency, and the home-based sleep studies are yielding meaningful data on the frequencies of OSA and NH. Our data is insufficient to be considered reportable, but we are on trajectory to meet all the specific aims of the proposal.

CONCLUSIONS

Our early data indicate that our home-based testing strategy will be a practical approach for diagnosing sleep-related breathing disorders in SCI patients. OSA will be very common, although it is too soon to project the exact prevalence. Likewise, NH will be detected with an appreciable frequency. It is premature to determine what clinical features, if any, will predict OSA, NH, or compliance with noninvasive ventilation. A large proportion of the projected 100 subjects will have to proceed through the 12 month follow-up protocol before we can identify any clinical benefits of noninvasive ventilation.

REFERENCES

We are too early in the protocol to have collected enough data for meaningful analysis and publication. However, we have recently submitted a manuscript describing the feasibility of home-based tc-pCO_2/SpO_2 monitoring, and this has been accepted for publication in the *Archives of Physical Medicine and Rehabilitation*, as cited below. We include this in the progress report because this manuscript describes the findings that constituted the preliminary data supporting the current project. Further, it is our first report to demonstrate the feasibility of tc-pCO_2/SpO_2 monitoring as a practical approach for diagnosing

NH in neuromuscular respiratory failure, as well as the high prevalence of unsuspected hypercapnia. Spinal cord injury was the most common diagnosis in this subject group.

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Home-Based Overnight Transcutaneous Capnography/Pulse Oximetry for Diagnosing Nocturnal Hypoventilation Associated with Neuromuscular Disorders

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4 Tables

1 Figure

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Home-Based Overnight Transcutaneous Capnography/Pulse Oximetry for Diagnosing Nocturnal Hypoventilation Associated with Neuromuscular Disorders

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We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated. We further certify that all financial and material support for this research is clearly identified in the title page of the manuscript.

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4 Tables

1 Figure

Reprints will not be available.

Abstract

Objective: To determine the utility of home-based, unsupervised transcutaneous (tc)-pCO_2/SpO_2 monitoring for detecting nocturnal hypoventilation (NH) in individuals with neuromuscular disorders.

Design: Retrospective case series, analyzed consecutively.

Setting: Multidisciplinary neuromuscular respiratory failure (NMRF) clinic at an academic institution.

Participants: 35 subjects (mean 46.9 yrs, 68.6% male) with spinal cord injury (45.7%) or other neuromuscular disorders underwent overnight tests with tc-pCO_2/SpO_2 monitoring. Fifteen (42.9%) were using nocturnal ventilatory support, either BiPAP or tracheostomy/ventilation (TV).

Interventions: A respiratory therapist brought a calibrated tc-pCO_2/SpO_2 monitor to the patient's home and provided instructions for data collection during the subject's normal sleep period. Forced vital capacity (FVC), body mass index (BMI) and exhaled end-tidal (ET)-pCO_2 were recorded at a clinic visit prior to monitoring.

Main Outcome Measures: Detection of NH (tc-pCO_2 ≥ 50 mmHg for ≥ 5% of monitoring time). Data was also analyzed to determine if nocturnal oxygen desaturation (SpO_2 ≤88% for ≥ 5% of monitoring time), FVC, BMI, or daytime ET-pCO_2 could predict the presence of NH.

Results: NH was detected in 18 subjects (51.4%), including 53.3% of those using BiPAP or TV. NH was detected in 43.8% of ventilator-independent subjects with normal daytime ET-pCO_2 (present for 49.4% ± 31.5 (mean ± SD) of the study period), and in 75% of subjects with an elevated daytime ET-pCO_2 (present for 92.3% ± 8.7 of the study period). O_2 desaturation, BMI and FVC were poor predictors of NH. Only 3 attempted monitoring studies failed to produce acceptable results.

Conclusions: Home-based, unsupervised monitoring with tc-pCO_2/SpO_2 is a useful method for diagnosing NH in NMRF.

Key words:

Blood Gas Monitoring, transcutaneous

Home Care Services, hospital-based

Neuromuscular Diseases

Hypoventilation

Sleep Apnea Syndromes

ABBREVIATIONS

ALS = amyotrophic lateral sclerosis; BiPAP = bilevel positive airway pressure; BMI = body mass index; ET-pCO_2= end-tidal partial pressure of carbon dioxide; FVC = forced vital capacity; NH = nocturnal hypoventilation; NIV = noninvasive ventilation; NM/other = neuromuscular disorders, other than spinal cord injury; NMRF = neuromuscular respiratory failure; OSA = obstructive sleep apnea; PSG = polysomnograms; SCI = spinal cord injury; SpO_2 = oxygen saturation by pulse oximetry; tc-pCO_2 = transcutaneous partial pressure of carbon dioxide; TV = tracheostomy ventilation

Neuromuscular respiratory failure (NMRF) is often managed with noninvasive ventilation (NIV) to forestall progression of hypercapnia, and to relieve dyspnea. Because nocturnal hypoventilation (NH) generally precedes daytime hypercapnia, the first indication for NIV may be transient rises in pCO_2 during sleep, even in the absence of obstructive sleep apnea (1-3). Recognizing NH early may have particular value, as any nocturnal pCO_2 reaching ≥ 50 mmHg marks a high probability of requiring NIV within two years (4). Additionally, initiating NIV based on symptomatic daytime hypercapnia results in improved mortality and quality of life in amyotrophic lateral sclerosis (ALS) (5). A practical, cost-effective method for early recognition of NH has yet to emerge. Currently available approaches include correlating NH with lung function parameters (1, 6, 7), polysomnograms (PSG) with exhaled pCO_2 monitoring (8), and arterial blood gas monitoring.

Current methods are limited in their ability to predict or detect NH, and to determine proper timing for initiating NIV. Pulmonary function parameters such as forced vital capacity (FVC) can predict the need for NIV in certain neuromuscular conditions, but they do not reliably predict hypercapnia (1, 6, 7). Nocturnal pCO_2 monitoring, either by arterial blood gases or end-tidal pCO_2 (ET-pCO_2) measurements, generally requires an inpatient study or an overnight stay in a sleep laboratory. It is problematic to assess outpatients with neuromuscular disorders for NH, as sleep laboratories often are ill-equipped to accommodate their special needs. Barriers to access and the inability to accommodate skilled caregivers impose daunting obstacles that, in our

experience, often cause patients to refuse overnight stays in sleep laboratories. Likewise, once nocturnal NIV is initiated, there are no established methods for longitudinal home-based monitoring to determine the effectiveness of positive pressure ventilation in achieving normocapnia.

We hypothesized that the barriers to performing PSG has led to under-recognition of NH in patients with neuromuscular disorders. In this study, we report our experience with using a monitor that measures transcutaneous pCO_2 and O_2 saturation by pulse oximetry (SpO_2) for unsupervised overnight studies in the home setting to detect NH in individuals with a variety of neuromuscular disorders.

METHODS

Informed Consent. Permission for retrospective analysis of patient medical records was granted for this study by Institutional Review Board, HUM00042079. The monitoring studies that were reviewed were performed between December 2009 and June 2011.

Patients. The study population consisted of patients seen at a multidisciplinary clinic for treatment of neuromuscular respiratory failure. These patients are managed jointly by a pulmonologist and a Physical Medicine and Rehabilitation specialist. The motor deficit of patients with spinal cord injury (SCI) was defined according to the International Standards for the Neurological Classification of Spinal Cord Injury (9).

Home-Based Monitoring. Monitoring was performed only when the patients were clinically stable for at least 4 weeks. A respiratory therapist brought a SenTec Digital Monitor[a] to the patient's home on the day of the study. This monitor measures and records transcutaneous partial pressure of carbon dioxide (tc-pCO_2), SpO_2, and heart rate. The therapist calibrated the monitor and attached the skin probe below the clavicle. The patient/caregivers were instructed to start recording at the beginning of the overnight sleep period, and to turn the monitor off when the patient awoke the following morning. The data was then downloaded and analyzed by V-

STATS software[a], employing automated drift-correction of the pCO_2 signal. The manufacturer's reported resolution is 1mmHg for pCO_2 and 1% for spO_2. Using this device to compare drift-corrected tc-pCO_2 to arterial pCO_2 in a sleep laboratory setting, there was close correlation (R=0.946) and agreement between measurements (range of differences -4.9 to +6.5 mmHg) (10). Bland-Altman analysis demonstrated that the discrepancy was > 7.5mmHg in only 1% of measurement pairs (10).

Pulmonary Function Testing. Spirometry was performed by a Pulmonary Function Laboratory equipped with MedGraphics spirometers[b]. Studies were performed according to guidelines published by the American Thoracic Society and European Respiratory Society (11). Predicted values were calculated according to standard reference equations (12).

End-tidal pCO_2 Measurements. A Tidal Wave 715A monitor[c] was used to measure ET-pCO_2 during outpatient evaluations when the patients were clinically stable.

Statistics. Comparisons between groups were made by t-tests for continuous variables, and X^2 for categorical variables. Simple logistic regression was used to predict the odds of nocturnal hypoventilation. p-values less than 0.05 were considered significant. All data analysis was performed on SAS® software, version 9.2.[d]

RESULTS

The characteristics of the study population are summarized in Table 1. The patients were 46.9 ± 16.6 (20-75) years old (mean ± SD, range), and 68.6% were male. Sixteen patients (45.7%) had SCI, and 68.8% of these had motor deficits at or above the C5 level. The time interval since SCI was 13.5 ± 10.8 (2-37) years (mean ± SD, range). Of the 19 patients in the NM/other category, 5 had multiple sclerosis, 2 each had ALS, cerebral palsy, or Duchenne's muscular dystrophy, and 6 had other miscellaneous diagnoses. Fifteen (42.9%) patients were already using nocturnal ventilatory support; BiPAP (10), or mechanical ventilation by tracheostomy (TV; 5).

The indications for overnight monitoring are summarized in Table 2. The most common reason for the study, in 16 cases (45.7%), was to determine if NH was present in patients with normal daytime ET-pCO_2 and moderate-severe restrictive ventilatory defects on spirometry, but not using nocturnal ventilatory support. In 4 (12.1%) cases, monitoring was performed to determine the severity of NH in patients known to have daytime hypercapnia (ET-pCO_2 47-55 mmHg), but not using ventilatory support. Fifteen (42.9%) studies were performed on patients using BiPAP/TV to determine if NH was adequately controlled.

Of the 38 overnight studies, 3 (8.6%) were determined to be unacceptable, either because of a technical problem (detached probe), unusually short sleep time, or unacceptably high pCO_2 signal artifact. Therefore, a total of 35 studies in 35 individuals are included in the final analysis. In the valid studies, data was recorded for a mean of 496.8 minutes (Table 1). There were no adverse events or patient complaints associated with the monitoring procedure.

Among the 16 normocapneic patients who were not using BiPAP/TV, NH was confirmed in 7, for an overall yield of 43.8% (Table 2). The % of the study time during which the pCO_2 was $\geq$ 50mmHg was 49.4% ± 31.5 (mean ± SD), ranging from 11- 97%. Peak pCO_2's ranged from 54-58 mmHg. Among the 4 patients with daytime hypercapnia and not using BiPAP/TV, 3 (75%) had NH and the pCO_2 was $\geq$ 50mmHg for 92.3% ± 8.7 (mean ± SD) of the study time, range 80-99%. Peak pCO_2's were 60-71 mmHg.

Fifteen (42.9%) of the patients were using BiPAP or TV at the time of the overnight study. In all cases, the primary indication for BiPAP/TV was respiratory failure, and not obstructive sleep apnea. The majority (60%) of patients using BiPAP/TV had NM/Other diagnoses, while only 27.6% had SCI, $p = 0.05$. NH was detected in 8 (53.3%) of these patients. The pCO_2 was $\geq$50mmHg for 74.3% ± 27.6 of the study time (mean ± SD), range 10-100%, and the peak pCO_2 ranged from 56-143 mmHg.

Next, we sought to determine whether clinical indicators such as body mass index (BMI), FVC, or nocturnal oxygen desaturation could predict the presence of NH. The BMI was measured within 3 months prior to the overnight study. Including all patients, the BMI in patients with NH confirmed by the overnight study was 27.4 $kg/m^2 \pm 8.5$ compared to 25.3 $kg/m^2 \pm 5.8$ without NH, $p = 0.4$. (Table 3). The FVC was measured within 6 months of the overnight study in 26 (74.3%) patients. Another 6 studies were excluded from this analysis (3 unable to perform spirometry, and not attempted in 3 because of disease progression). The FVC in those with NH was 35.2 ± 12.1 % predicted, compared to 36.6% ± 12.3 without NH, $p = 0.77$. Scatter plots of the BMI, motor level, and FVC provide more detailed individual information for the spinal cord injury group (Figure 1). Lastly, nocturnal oxygen desaturation (SpO_2 <88% for >5% of study time), was found in 6 (33.3%) patients with, and in 5 (29.4%) without NH $p = 0.8$. We also applied simple logistic regression analyses to determine if these clinical and laboratory features could predict NH (Table 4). Including all studies, the only predictor of NH is elevated daytime ET-pCO_2, OR 1.21 (95% CI 1.04,1.41, $p = 0.01$). Because nocturnal ventilatory support probably prevented some instances of NH or O_2 desaturation, we performed separate simple logistic regressions for patients not using nocturnal ventilatory support, and those using nocturnal BiPAP/TV. Only in the latter group did daytime ET-pCO_2 predict the likelihood of NH (Table 4). We note that the present study included patients with a variety of underlying diagnoses, and only patients with spinal cord injury were represented in significant numbers. Future studies focusing on specific underlying diagnoses will be necessary to determine whether reliable clinical predictors for nocturnal hypoventilation can be identified for specific neuromuscular disorders.

DISCUSSION

Nocturnal hypoventilation is a well-recognized complication of many neuromuscular disorders. Current diagnostic studies are limited for this population, due to both study characteristics and logistics. Our data highlights that in patients with neuromuscular disorders, NH is common and under-recognized, and that easily accessible parameters such as BMI, FVC, and O_2 desaturation do not reliably predict its presence. We also demonstrate that patients on home nocturnal ventilation for NMRF frequently do not achieve normocapnia. These findings establish a role for home-based, unsupervised overnight tc-pCO_2/SpO_2 monitoring in the care of patients with NMRF.

Physicians recognize that they should be vigilant for emerging NMRF (2, 3, 13), but it can develop over any time frame, due to worsening of the underlying disorder, age-related decline in lung function, worsening scoliosis, chest wall ankylosis, and the cumulative effects of respiratory infections (3). In SCI, most patients remain stable after liberation from ventilatory support during their initial hospitalization, while a decline in pulmonary function has been documented in some patients as much as 10-20 years later (14, 15). Likewise, late development of hypercapnia has been described (16). Therefore, patients are often living at home when their pulmonary function is declining. By this time, they are often highly resistant to hospitalization,

or to overnight stays in a sleep laboratory where their specialized needs are difficult to accommodate.

The decision to begin NIV is complex, as it involves several interrelated problems, any of which may be an indication for ventilatory support (2, 3, 17). While NIV does not improve pulmonary function or respiratory muscle strength in the long term (18, 19), it does provide short-term relief of dyspnea and enables the patient to sleep without nocturnal pCO_2 retention or frequent arousals. It remains uncertain whether clinical outcomes can be optimized by using spirometry or indices of respiratory muscle strength as the primary indicator for starting NIV (1-3, 7, 8, 20, 21). The complexity of this problem is compounded by the observation that the physiologic status of patients at the onset of NIV may vary, depending on the underlying diagnosis (22). In the present study, FVC was a poor predictor of NH in all patient groups (Table 4). Thus, while spirometry may predict the utility of NIV for some patients, it does not follow that it will specifically identify patients with nocturnal hypercapnia. NIV may also be initiated to interrupt an escalating cycle of hypercapnia, oxygen desaturation, atelectasis, and recurrent infections. Any degree of NH can predict progression to requiring NIV support within months (4). Later intervention, when symptomatic daytime hypercapnia has developed, has been shown to improve short-term mortality and quality of life in ALS (5). It remains to be determined whether these clinical benefits are conferred, or even magnified, if NIV is begun while hypercapnia only occurs during sleep. If so, early detection of hypercapnia by overnight monitoring would clearly be preferable to daytime assessments.

Thus far, transcutaneous capnography has been used mostly in inpatient settings (10, 23-27). It has also been an effective tool for managing acute-on-chronic respiratory failure with BiPAP (28), and as an adjunct to PSG performed in a sleep laboratory (10). Our study confirms that recording transcutaneous capnography, in this case the SenTec Digital Monitor, can also be used effectively for unsupervised overnight monitoring in the outpatient setting. Home-based, continuous transcutaneous pCO_2 monitoring has several advantages. First, it may be the only method for assessing patients that refuse testing in a sleep laboratory. Secondly, home-based testing may provide a more authentic assessment during the patient's usual sleep patterns, whereas a sleep laboratory setting could undermine the patient's normal sleep by disrupting their schedule, providing an unfamiliar or unsuitable bed, or altering the patient's use of medications or alcohol. Spot checks of pCO_2 by any method would be susceptible to sampling error if hypercapnia is transient. Continuous monitoring of ET-pCO_2 in the home may require frequent adjustments by a technician, which may disrupt sleep and add considerably to the cost of the study. Monitoring pCO_2 levels without disturbing the patient's sleep would be critical to assess NH and properly titrate BiPAP. Lastly, ET-pCO_2 may not accurately reflect arterial CO_2 in the presence of mask leakage or parenchymal lung disease (24, 29). Home-based continuous monitoring by transcutaneous capnography would circumvent these problems.

The last, and least studied, indication for beginning NIV is to prevent adverse systemic effects of hypercapnia. There is substantial evidence that obstructive sleep apnea (OSA) confers greater risks for mortality, myocardial infarction, hypertension, stroke, and glucose intolerance (30-32). Presently, we do not know the extent to which hypercapnia in the absence of OSA is associated with these same risks. If the systemic effects of NH are similar to those of OSA, then

early recognition of NH should be preferable to waiting until daytime hypercapnia develops. It is notable that in our patients, NH could not be predicted by nocturnal oxygen desaturation or the severity of pulmonary restriction (Tables 3 and 4), supporting the concept that while dyspnea, atelectasis, and nocturnal hypercapnia are highly interrelated, none of these can stand alone as the justification for starting NIV(17). Thus, overnight transcutaneous capnography provides complementary data that can facilitate the decision-making process to start NIV. In addition, overnight transcutaneous capnography/pulse oximetry can be used to monitor the effectiveness of BiPAP or mechanical ventilator settings for the treatment of NMRF.

LIMITATIONS

We acknowledge several weaknesses and limitations to this study. First, the retrospective design may have significantly influenced the reported prevalence of NH. Most of the studies we performed were part of an initial assessment at a multidisciplinary clinic for management of NMRF, occurring at a point when most patients already had severe pulmonary restriction. The yield of these studies can be expected to vary considerably, depending on the patient mix and the timing of the studies. Next, it is critical to note that our study specifically addresses NH, and not OSA, so tc-pCO_2 monitoring cannot be used as a substitute for PSG, just as PSG are generally configured to diagnose OSA/central sleep apnea, and not NH (33). Depending on the underlying diagnosis, OSA and NH may coexist frequently, so neither overnight tc-pCO_2 monitoring nor standard PSG alone can be expected to fully characterize sleep-related breathing disorders. We cannot compare the reliability, accuracy, or cost effectiveness of the SenTec monitor used in the

present study with similar devices from other manufacturers. Lastly, a cost/benefit analysis will remain incomplete until the long-term costs of ventilatory support initiated because of this monitoring strategy, as well as the long-term health benefits/risks, can be quantitated.

CONCLUSIONS

Home-based overnight monitoring with transcutaneous capnography/pulse oximetry is a practical method for detecting nocturnal hypoventilation in patients with spinal cord injury. Nocturnal hypercapnia is common, even in patients with normal daytime pCO2 levels, and in patients already receiving ventilatory support. Nocturnal hypercapnia cannot be predicted accurately by recent spirometry, BMI, or nocturnal oxygen desaturation.

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Suppliers

a. SenTec AG; Therwil; Switzerland

b. MedGraphics; St. Paul; MN

c. Phillips; Respironics Inc; Murrysville, PA

d. SAS Institute Inc. Cary, NC

FIGURE LEGEND

Figure 1. Characteristics of patients with spinal cord injury. LEFT: Scatter plot of the forced vital capacity (FVC), expressed as % predicted, stratified by the absence (NH-) or presence (NH+) of nocturnal hypoventilation determined by overnight transcutaneous capnography. RIGHT: Scatter plot of the distribution of motor deficit level and body mass index (BMI), with each symbol representing a single patient. ■NH- ● NH+

Table 1-- *Patient Characteristics (n=35)*

Age (years)		46.9 ± 16.6 (20-75)
Gender	Male	24 (68.6%)
	Female	11 (31.4%)
Diagnosis	Spinal Cord Injury	16 (45.7%)
	Neuromuscular Disease/Other	19 (54.3%)
	Multiple Sclerosis	5
	Amyotrophic Lateral Sclerosis, Duchenne's Muscular Dystrophy, Myotonic Dystrophy, Cerebral Palsy	2 each 1 each
	Scoliosis, Kennedy's Disease, Obesity Hypoventilation, Myelocele, Congenital Central Hypoventilation, Traumatic Brain Injury	
Forced Vital Capacity (% predicted)		36 ± 11.8 (17-58)
Body Mass Index (kg/M^2)		26.4 ± 7.2 (13-48.3)
Duration of Overnight Monitoring (minutes)		496.8 ± 106.6 (230-664)

Data are expressed as n (%) or mean ± SD (range)

Duration of Monitoring excluded 2 studies where monitoring was not terminated as instructed

Table 2--*Prevalence and Severity of Nocturnal Hypercapnia, Stratified by Indication for Monitoring*

Indication for Overnight Transcutaneous pCO_2/ Pulse Oximetry Monitoring	Nocturnal Hypoventilation	% of Monitoring Time with tc- $pCO_2 \geq 50$ mmHg	Peak pCO_2 (mmHg)
I. Determine whether nocturnal hypercapnia or oxygen desaturation is present (patients with daytime ET-$pCO_2 < 47$ mmHg, and not using nocturnal ventilatory support) n = 16 (45.7%)	7 (43.8%)	49.4 ± 31.5 (11 - 97)	55.6 ± 1.9 (54 - 58)
II. Determine the severity of nocturnal hypercapnia or oxygen desaturation (patients with daytime ET-$pCO_2 \geq 47$ mmHg, and not using nocturnal ventilatory support) n = 4 (12.1%)	3 (75%)	92.3 ± 8.7 (80 - 99)	66.1 ± 4.6 (60 - 71)
III. Determine the effectiveness of TV/BIPAP in preventing nocturnal hypercapnia or oxygen desaturation n = 15 (42.9%)	8 (53.3%)	74.3 ± 27.6 (10 - 100)	76.5 ± 29.7 (56 - 143)

Data are expressed as n (%) or mean ± SD (range)
tc = transcutaneous. Nocturnal hypoventilation = tc-$pCO_2 \geq 50$ mmHg for ≥ 5% of monitoring time

Table 3--*Predictors of Nocturnal Hypoventilation*

	All Patients	Patients without NH	Patients with NH	p-value
	n=35	n=17	n=18	
Age	46.9 (16.6)	45.4 (17.6)	48.4 (16.0)	0.60
Gender				
Male	24 (68.6%)	11 (64.7%)	13 (72.2%)	0.63
Female	11 (31.4%)	6 (35.3%)	5 (27.8%)	
Diagnosis				
SCI	16 (45.7%)	6 (35.3%)	10 (55.6%)	0.23
NM/Other	19 (54.3%)	11 (57.9%)	8 (42.1%)	
Use of BIPAP or TV	15 (42.9%)	7 (41.2%)	8 (44.4%)	0.85
Body Mass Index	26.4 ± 7.3	25.3 ± 5.8	27.4 ± 8.5	0.40
Forced Vital Capacity (% predicted)	36.0 ± 12.0	36.6 ± 12.3	35.2 ± 12.1	0.77
Daytime SpO_2 (%)	96.4 ± 2.2	97.1 ± 1.95	95.8 ± 2.3	0.10
Presence of nocturnal oxygen desaturation	11 (31.4%)	5 (29.4%)	6 (33.3%)	0.80
Daytime ET-CO_2 (mmHg)	43.9 ± 5.5	41.3 ± 4.6	46.3 ± 5.4	0.006
Daytime ET-CO_2 > 47 mmHg	14 (40%)	4 (23.5%)	10 (55.6%)	0.05

Data are expressed as n (%) or mean ± SD

NH = Nocturnal hypoventilation = transcutaneous-$pCO_2 \geq 50$ mmHg for ≥ 5% of monitoring time

Oxygen desaturation defined as $SpO_2 \leq 88\%$ for ≥5% of monitoring time

BiPAP = bilevel positive airway pressure ventilation, TV = tracheostomy/mechanical ventilation

SpO_2 = oxygen saturation by pulse oximetry

ET-pCO_2 = end-tidal partial pressure of CO_2

Statistical analysis: Comparisons between groups were made by t-tests for continuous variables and X^2 tests for categorical variables

p values are for comparisons of patients with NH, vs. without NH

Table 4--*Simple Logistic Regressions for Prediction of Nocturnal Hypoventilation*

	All Patients			No Nocturnal Ventilatory Support (n=20)			Using Nocturnal Ventilatory Support (n=15)		
	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI
Age (years)	0.59	1.01	0.97, 1.05	0.82	0.99	0.94, 1.05	0.32	1.03	0.97, 1.10
Male Gender	0.63	1.42	0.34, 5.94	0.34	2.67	0.36, 19.7	0.72	0.67	0.08, 5.88
BMI	0.40	1.04	0.95, 1.15	0.71	1.03	0.89, 1.19	0.44	1.06	0.92, 1.21
SCI Diagnosis	0.23	2.29	0.59, 8.94	0.37	2.33	0.37, 14.6	0.33	3.60	0.28, 46.4
FVC	0.76	0.99	0.93, 1.06	0.93	1.00	0.93, 1.08	0.59	0.96	0.82, 1.12
SpO_2	0.11	0.74	0.52, 1.06	0.73	1.13	0.57, 2.27	0.07	0.62	0.37, 1.03
ET-pCO_2	0.012	1.21	1.04, 1.41	0.14	1.17	0.95, 1.45	0.04	1.25	1.01, 1.56

OR (odds ratio) = fold-increase in odds of having NH for each 1 point rise for a continuous variable, or yes vs. no for a categorical variable. CI = Confidence Interval

Nocturnal hypoventilation = transcutaneous-$pCO_2 \geq 50$ mmHg for $\geq 5\%$ of monitoring time.

BMI = Body Mass Index, SCI = Spinal Cord Injury

SpO_2 = oxygen saturation by pulse oximetry, ET-pCO_2 = end-tidal partial pressure of CO_2

FVC = Forced Vital Capacity (% predicted)

FVC studies excluded if performed > 6 months before pCO_2/SpO_2 monitoring: all patients, n = 26; no ventilatory support, n = 16; using ventilatory support, n = 10

Figure 1